Exhibit B

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Prodrug approaches to the improved delivery of peptide drugs. [Review] [168 refs] Source
Current Pharmaceutical Design. 5(4):265-87, 1999 Apr. Abstract
Undesirable pharmaceutical and biopharmaceutical properties, which include low water solubility, poor stability, and low permeability through biological membrane barriers, often hinder the clinical development of biologically active peptides. Finding solutions to these problems is a contemporary issue in developing clinically the vast number of biologically active peptides as drugs. In recent years, significant progress has been made in developing prodrug approaches for the improvement of the water solubility, stability, and membrane permeability of peptides. For improving water solubility, the focus has been on the bioreversible introduction of ionizable functional groups to peptides, which helps to increase the polarity and thus water solubility of the peptide drugs. For improving stability, efforts have focused on stabilizing peptides against exopeptidase-mediated hydrolysis by bioreversibly masking the terminal carboxyl and/or amino groups. For improving permeability thr! ough biological barriers, recent efforts have focused on both improving the lipophilicity of a peptide in order to facilitate its passive permeation through biological membranes and conjugation of a peptide to a carrier which allows for the active transport of the peptide-carrier conjugate. Many of the prodrug systems developed recently have the potential to be used clinically for the delivery of peptide drugs to the desired site of action. [References: 168]